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Barbiturate Intoxication

Morbidity and Mortality

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The complications encountered in caring for 185 patients intoxicated with barbiturates were reviewed. The population consisted of 142 patients with long-acting barbiturate concentrations of 8 mg per 100 ml or greater, 20 patients with short-acting barbiturate concentrations of 3 mg per 100 ml or greater and 23 consecutive patients with short-acting barbiturate intoxication referred for monitoring. Pneumonia was the major cause of morbidity and mortality and correlated best with the initial depth of coma and the use of an endotracheal tube in treatment. Cardiovascular instability manifested by pulmonary edema was the next leading cause of morbidity and mortality and correlated best with the initial depth of coma and the quantity of intravenous fluid administered. In retrospect, use of eliminative measures such as dialysis would probably not have altered the outcome in most of the patients who died and attempts at forced diuresis may have contributed to several deaths. Particular emphasis should be placed on the problems of sepsis and fluid therapy in the management of these patients.

CURRENT RECOMMENDED therapy for the treatment of barbiturate intoxication consists of meticulous supportive care[1-5] with or without aggressive measures to remove barbiturate from the body[6-13] (gastric lavage, forced diuresis, peritoneal dialysis and hemodialysis). An unexpectedly frequent occurrence of pneumonia and fluid overload in those patients who were severely intoxicated prompted a critical review of the current therapy for barbiturate intoxication at the Los Angeles County-University of Southern California (LAC-USC) Medical Center. In an attempt to evaluate the cases of the most severely intoxicated patients, one group with long-acting and one with short-acting barbiturate intoxications were retrospectively selected on the basis of potentially lethal serum barbiturate concentrations.[14-15] To better document fluid overload, a limited prospective study was undertaken involving more careful monitoring of cardiovascular function.

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Methods

The clinical course and laboratory data of the following patients admitted to hospital for barbiturate intoxication at LAC-USC Medical Center were grouped and analyzed as follows: *Group I*

ABBREVIATIONS USED IN TEXT

CPK = creatine phosphokinase
LAC-USC = Los Angeles County-University of Southern California (medical center)
LDH = lactic dehydrogenase
LDH_1, LDH_2, LDH_5 = serum cardiac LDH isoenzymes
SGOT = serum glutamic oxaloacetic transaminase

—142 patients with serum long-acting barbiturate concentrations of 8 mg per 100 ml or greater on admission, *Group II*—20 patients with serum short-acting barbiturate concentration of 3 mg per 100 ml or greater on admission and *Group III*—23 consecutive patients referred for short-acting barbiturate intoxication (0.2 to 4.3 mg per 100 ml) who were prospectively studied. Cases were located by reviewing the LAC-USC Medical Center toxicology records in Groups I and II, or by referral for Group III. In all patients admitted with a suspected drug overdosage, a hypnotic screen and determination of blood barbiturate levels are routinely done.

All cases were grouped into the admitting stage of coma after an adequate airway was established.[16] The coma stages were:

- *Stage 0*—Not in coma.
- *Stage 1*—Response to painful stimuli. Deep tendon reflexes present. Gag reflex. Blood pressure normal and stable. Respiration adequate.
- *Stage 2*—No response to painful stimuli. Deep tendon reflexes present. Blood pressure normal and stable. Respiration adequate but slow rate.
- *Stage 3*—No response to painful stimuli. Deep tendon reflexes absent. Gag reflex present or absent. Respiration adequate but slow rate.
- *Stage 4*—No response to painful stimuli. Deep tendon reflexes absent. Blood pressure unstable and needs support or respiration inadequate and needs support or both.

Pneumonia was diagnosed by the criteria of fever, leukocytosis, purulent sputum and an infiltrate on x-ray film of the chest; specific bacteriologic diagnosis was not required. Antibiotics were administered only after pneumonia or other bacterial infection was evident. Endotracheal intubation was routine during gastric lavage to protect the airway. Intubation was also carried out when necessary to improve bronchopulmonary toilet and provide respiratory support. Hospital policy recommended gastric lavage and lavage was carried out in most patients in Stage 1 through 4 coma.

Cardiovascular instability was diagnosed by any of the following criteria: protodiastolic ventricular gallop (S_3), central venous pressure over 10 cm of water measured with the respirator disconnected or findings on an x-ray film of the chest showing either redistribution of pulmonary arterial flow to the upper lobes or gross pulmonary edema.

Serum barbiturate concentrations were determined at the LAC-USC Medical Center spectrophotometrically by a modification of the method of Goldbaum.[17] Whole blood counts were determined by Coulter counter. Serum glutamic oxaloacetic transaminase (SGOT) was determined by the method of Karman, Wroblewski and LaDue[18] with results expressed in Wroblewski-LaDue units. Alkaline phosphatase was determined by the method of Bessey, Lowry and Brock[19] and expressed in Bessey-Lowry units. Aldolase was measured enzymatically by BioScience Laboratories.[20] Lactic dehydrogenase (LDH) was measured by the Trayser-Seligson modification of the Wroblewski-LaDue method[21] and expressed in Henry units. LDH isoenzymes were determined by the method of DiGiorgio.[22] The percentages were normalized by multiplying each fraction by the total LDH. Creatine phosphokinase (CPK) was assayed by the Rosalki method[23] and expressed in Henry units. Statistical analysis was done by the method of analysis of variance and trend analysis for populations of three or more groups.

TABLE 1.—*Long-Acting Barbiturate Concentrations of 8 mg per 100 ml or Greater*

Stage	Number of Patients	Age	Barbiturate Range	Barbiturate Average±S.D.
0	70	1-69	8-20	10.53±2.50
1	34	5-53	8.1-16	10.22±2.17
2	13	26-51	8.2-31.1	13.59±6.40
3	16	14-83	8.2-22.7	13.64±4.76
4	9	18-50	12-31.7	22.16±6.13

TABLE 2.—*Incidence of Temperature >100°F, Pneumonia and Death in Patients with Long-Acting Barbiturate Concentrations of 8 mg per 100 ml or Greater*

Stage	Number of Patients	Temp >100°F	Pneumonia	Deaths
0	70	6 (9%)	3 (4%)	0
1	34	11 (32%)	3 (9%)	0
2	13	11 (85%)	10 (77%)	1 (8%)
3	16	15 (94%)	12 (75%)	2 (12%)
4	9	9 (100%)	9 (100%)	1 (11%)
	142	52 (37%)	37 (26%)	4 (3%)

TABLE 3.—*Cardiovascular Instability Correlated with Intravenous Fluids Exceeding 240 ml per Hour for Patients with Long-Acting Barbiturate Concentrations of 8 mg per 100 ml or Greater*

Stage	Number of Patients	Instability	Instability >240 ml/hr	Instability <240 ml/hr
0	70	1 (1%)	0/1	1/69 (1%)
1	34	1 (3%)	1/3 (33%)	0/31
2	13	1 (8%)	1/5 (20%)	0/8
3	16	3 (17%)	3/9 (33%)	0/7
4	9	6 (67%)	6/7 (86%)	0/2
	142	12 (9%)	11/25 (44%)	1/117 (1%)

TABLE 4.—*Short-Acting Barbiturate Concentrations of 3 mg per 100 ml or Greater*

Stage	Number of Patients	Age	Barbiturate Range	Barbiturate Average±S.D.
0	1	22	4.5	4.50
1	1	29	4.1	4.10
2	5	13-40	3.0-3.8	3.36± .34
3	5	20-55	3.1-5.2	3.82± .74
4	8	1-41	3.3-7.5	4.66±1.28

The cases in Group III were studied in greater detail to evaluate cardiovascular and metabolic function. In addition to the data collected for the other groups, each subject had the following data monitored and analyzed: highest body temperature, admission and peak serum CPK, LDH and LDH isoenzymes, aldolase, barbiturates, arterial oxygen pressure (Po_2) on admission, venous lactate, hemoglobin, and daily electrocardiograms (EKG's). The EKG's were read by one of the authors (B.H.B.) without knowledge of the clinical course and scored as normal or abnormal on the basis of QRS-T morphology. The patients in Stage 2 and Stage 3 coma were deleted from statistical analysis because of their small number.

Results

Group I—Long-acting barbiturate, 8 mg per 100 ml or greater

The patients' ages ranged from 1 to 83 years and were equally distributed among the stages of coma. There was a large overlap between the serum barbiturate concentrations in each stage of coma (Table 1).

During time in hospital, pneumonia and a temperature above 100°F (37.8°C) were more common as the stage of coma increased ($p<.01$) (Table 2). One patient in Stage 1 coma, six of 13 in Stage 2, nine of 16 in Stage 3, and all nine patients in Stage 4 were endotracheally intubated. In 24 of these 25 patients, pneumonia developed. In 13 of the 117 patients not intubated pneumonia developed—3 not in coma, 2 in Stage 1, 3 in Stage 2 and 5 in Stage 3 ($p<.001$) (Figure 1). The number of days the patients remained intubated did not correlate with drug concentration ($r=.3$, p=n.s. [r is the correlation coefficient; p is the probability; n.s. means not significant]).

TABLE 5.—*Incidence of Temperature of 100°F, Pneumonia and Death in Patients with Short-Acting Barbiturate Concentrations of 3 mg per 100 ml or Greater*

Stage	Number of Patients	Temperature 100°F	Pneumonia	Death
0	1	0	0	0
1	1	0	0	0
2	5	4 (80%)	2 (40%)	0
3	5	4 (80%)	2 (40%)	0
4	8	8 (100%)	8 (100%)	1 (13%)
	20	16 (80%)	12 (60%)	1 (5%)

In 11 of 25 patients who received more than 240 ml per hour of intravenous fluid for at least eight hours, signs of cardiovascular instability (as previously defined) were recorded. In only one of 117 patients who received less than 240 ml per hour were such signs recorded ($p<.05$) (Table 3).

One patient in Stage 2, two in Stage 3 and one in Stage 4 died. Three deaths were due to pneumonia and one was due to pulmonary edema. The death due to pulmonary edema occurred in a 45-year-old man in Stage 2 coma (8.2 mg per 100 ml serum concentration) who received 250 ml per hour of alkalinized intravenous fluid for 24 hours. Autopsy confirmed pulmonary edema as the only significant pathological feature.

Group II—Short-acting barbiturate, 3 mg per 100 ml or greater

Neither the patients' ages (range 1 to 55 years) nor the serum barbiturate concentration (range 3.0 to 7.5 mg per 100 ml) was significantly different among the coma stages (Table 4). The incidence of pneumonia and temperature above 100°F increased as the stage of coma deepened ($p<.05$) (Table 5). The number of days the patients remained intubated did not correlate with the serum barbiturate concentration ($r=.47$, p=n.s.). In 12 of 16 intubated patients, pneumonia developed while it developed in none of the four nonintubated patients ($p<.05$) (Figure 2). Cardiovascular instability was recorded in four patients, all in Stage 4 coma, aged 17, 30, 31 and 33 years. One patient in this group died because of pneumonia.

Group III—Short-acting barbiturates

The patients' ages ranged from 17 to 67 years and did not differ among the stages. Of the 23 cases of short-acting barbiturate intoxication, six were in Stage 1 coma, two in Stage 2, two in Stage 3 and 13 in Stage 4. The Stage 4 patients were classed in subgroups by absence (4A) or presence (4B) of cardiovascular instability using the previously mentioned criteria.

Mean serum barbiturate concentration was different for these stages when analyzed by variance and trend analysis in the ascending order of 1, 4A and 4B ($p<.05$) (Table 6). The serum cardiac isoenzyme concentrations (LDH 1 and LDH 2) were likewise statistically weighted to group 4B ($p<.05$) (Table 7). Moreover, in all eight of the patients in 4B, there were abnormal findings on electrocardiograms characterized by S-T segment changes; but in only one of six patients in Stage 1 were there abnormal findings on electrocardiograms. Similarly, the incidence of pneumonia and temperatures above 100°F increased with higher levels of coma ($p<.05$) (Table 6). The mean LDH, CPK, SGOT, LDH_5 and aldolase values were higher in the 4B patients, but failed to reach statistical significance ($.1>p>.05$) (Table 7).

The patients' admission arterial Po_2 measured while breathing room air ranged from 72 to 37 mm of mercury and did not correlate with stage of coma. None of these patients died.

In all but one of these patients there was a fall in hemoglobin concentration during one to five days in hospital. The mean initial hemoglobin concentration was 14.39 grams per 100 ml±.46 (S.E.M.) and the lowest mean concentration was 12.16 grams per 100 ml ($p<.01$). In none of these patients was there gastrointestinal blood loss or evidence of hemolysis. Phlebotomy never exceeded 80 ml on admission or 40 ml on each subsequent day. The total fall in hemoglobin correlated with the number of days until the nadir of the hemoglobin concentration occurred (Figure 3) ($r=.71$, $p<.05$). The largest falls occurred in the 48 patients.

Pooled data from Groups I through III

In both short- and long-acting barbiturate intoxication, the incidence of pneumonia increased with the initial depth of coma. For both intoxications the use of an endotracheal tube correlated with a greater incidence of pneumonia. Despite the generally shorter duration of coma for short-acting barbiturate intoxication, the incidence of pneumonia is comparable regardless of the drug or duration of coma when one simply considers the initial stage of coma (Figures 1, 2). Of the 63 cases of pneumonia in the entire series, the following aerobic bacterial sputum isolates were noted in 19: Staphylococcus aureus, 7; Escherichia coli, 3; Klebsiella, 3; Serratia, 1; Pseudomonas aerogenes, 2; Streptococcus faecalis, 1, and Enterobacteriaceae, 3.

Discussion

Pneumonia, cardiovascular instability and high serum barbiturate concentrations are uniform problems regardless of the type of barbiturate ingested. For this reason, the data are discussed in terms of major problems rather than separating the short- from the long-acting barbiturate intoxications. Parallel incidences of each problem in each group occurred in this series.

• *Pulmonary infection* is the major cause of morbidity and mortality in all groups. The aerobic bacterial organisms cultured are typically virulent and mixed. At the time of study, effective means of anaerobic culturing were not available; such data may be quite relevant.[24] Potential factors contributing to pneumonia include prior aspiration,[25] inadequate tracheal toilet, prolonged respi-

TABLE 6.—*Coma Stage Compared with Serum Short-Acting Barbiturate Concentration and Other Clinical Variables*

	Stage 1	*Stages 2-3*	*Stage 4A*	*Stage 4B*
Number of patients	6	2 stage 2 2 stage 3	5	8
Age±S.E.M.	36±6	22±3	29±5	34±6
Sex	4M—2F	1M—3F	2M—3F	4M—4F
Barbiturate concentration (per 100 ml)*	1.1±.2	2.5±.4	1.8±.2	2.7±.4
Pneumonia	1	2	1	3
Temperature 100°F	1	2	1	3
Patients intubated	1	3	5	8
Cardiovascular instability	0	0	0	8

*Probability .05.

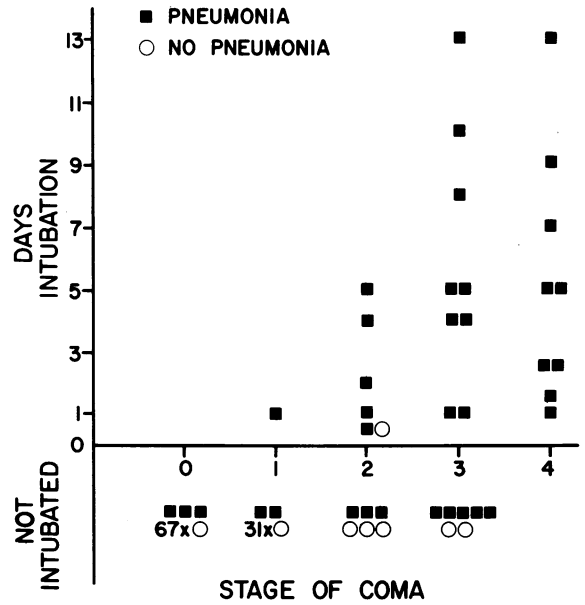

Figure 1.—Presence of pneumonia correlated with stage of coma and days of intubation for long-acting barbiturate concentrations of 8 mg per 100 ml or greater (probability <.001).

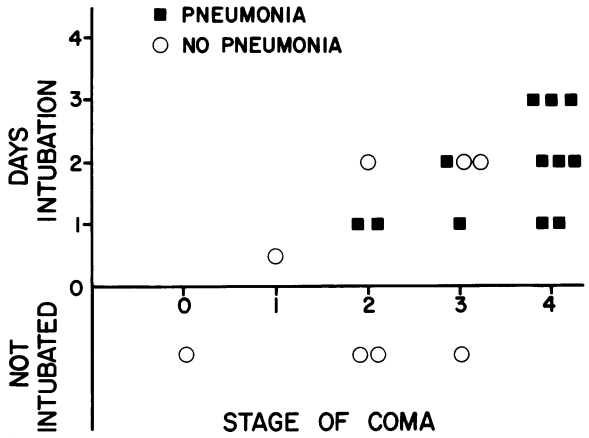

Figure 2.—Presence of pneumonia correlated with stage of coma and days of intubation for short-acting barbiturate concentrations of 3 mg per 100 ml or greater.

rator dependence, nosocomial contamination,[26] and perhaps unknown defects in host defense mechanisms secondary to the insult of intoxication, hypoxia and hypotension. Some of these patients may have also ingested alcohol, which has been shown to inhibit phagocytic activity.[27-29] It is unknown whether barbituric acid alone can alter phagocytic function.

The striking incidence of pneumonia seen in the endotracheally intubated patients (96 percent in Group I, 75 percent in Group II and 35 percent in Group III) compared to the nonintubated patients (11 percent in Group I, 0 percent in Group II and 17 percent in Group III) can be interpreted two ways. First, it is possible that the care of these patients was inadequate to prevent pneumonia. The data of Haberman and coworkers[30] documenting the difficulty of performing adequate tracheal suctioning through an endotracheal tube is pertinent to this issue. Second, the severity of the illness necessitating the intubation indicates that these patients were prime candidates for a prior aspiration[31] or subsequent pneumonia. These two possibilities cannot be differentiated from the data.

Although in the patients with short-acting barbiturate intoxication there was a shorter duration of coma than in those with long-acting intoxication, the incidence of pneumonia was comparable for each stage of coma. The only factors that correlated with pneumonia were the initial stage of coma and the use of an endotracheal tube in management. However, use of an endotracheal tube is usually necessary in Stage 4 coma and

TABLE 7.—*Coma Stage Compared with Laboratory and Electrocardiographic Changes*

	Stage 1	*Stages 2-3*	*Stage 4A*	*Stage 4B*
Number of patients	6	4	5	8
P_{O_2} (mm Hg) ±S.E.M.	59±7	54±8	56±4	54±2
Lactate (mg per 100 ml)	35±22	16±5	10±4	28±19
CPK(initial) (Henry units)	12±7	2.6±1.0	1.8±.6	231±180
CPK(maximum)	14±10	15±7	2.4±.7	346±183
LDH(maximum) (Henry units)	451±62	500±78	408±32	1,746±427
LDH_1 (Henry units)*	101±11	96±8	80±16	154±19
LDH_2*	115±16	151±26	117±10	220±37
LDH_5†	77±19	96±18	53±11	371±139
SGOT (Wroblewski-La Due units)†	36±11	38±11	38±12	493±254
Alkaline phosphatase (Bessey-Lowry units)	2.3±.4	2.9±.4	2.7±.1	3.9±.7
Aldolase†	47±8	38±7	35±6	266±101
Patients with abnormal findings on EKG's*	1	0	2	8

*Probability <.05.
†Probability <.1.
P_{O_2}=arterial oxygen pressure
CPK=creatine phosphokinase
LDH=lactic dehydrogenase
LDH_1, LDH_2 LDH_5=serum LDH isoenzymes
SGOT=serum glutamic oxaloacetic transaminase
EKG=electrocardiogram

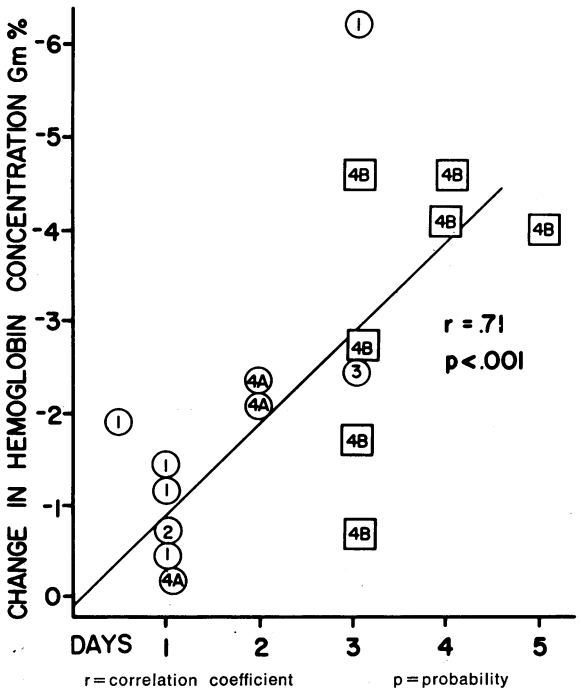

Figure 3.—Decrease from admission hemoglobin concentration correlated with the number of days until this lowest value occurred. Each patient is represented by his admission level of coma. Patients in Stage 4B showed signs of cardiovascular instability.

may be indicated in less severely intoxicated patients.

Prior aspiration or the total host insult seems to make pneumonia almost a certainty for the severely intoxicated intubated patient even if he remains in coma only 24 hours, as was the case in several Stage 4 short-acting barbiturate intoxications. Early in the hospital course, a patient's temperature exceeding 100°F should alert the physician to the likelihood of a developing pneumonia. Whether this is initially a chemical pneumonia or an actual bacterial pneumonia is unknown, but in most of the patients true bacterial pneumonia was eventually seen.

• We have observed a group of patients who have clinical manifestations of *fluid volume overload* and diffuse interstitial fluid accumulation including lung, abdominal viscera and skin. Depth of coma and the quantity of administered intravenous fluid are the major predisposing factors. Frequent weight determinations as well as careful attention to records of intake and output should improve clinical management.

The data suggest three potential cardiovascular defects which might explain why in these patients interstitial edema accumulates. First, there may be myocardial function impairment[32] in severely intoxicated patients stemming from the total overdose insult, or rarely, underlying organic heart disease. The significant leak of cardiac LDH isoenzymes and the frequency of abnormal findings on electrocardiograms in patients in whom there is inability to handle a fluid load (240 ml per hour) infers acute cardiac impairment. Despite the liberal criteria we have employed for cardiovascular instability, the circumstantial evidence is highly suggestive of inadequate myocardial function. Shubin and Weil[33] have previously rebutted the supposition that the initial hypotension seen in most of these patients reflects pump failure by showing that their cardiac index rises to "normal" with volume replacement. It is noteworthy that after volume replacement their fatalities had a significantly lower cardiac index, mean arterial pressure and urinary output than those who survived.[34] We can only reconcile our two conclusions by suggesting that a "normal" cardiac index is probably inadequate for these patients who are frequently septic, febrile, hypotensive and undergoing a fluid challenge.

Second, Shubin and co-workers[33] have suggested that the venous capacitance bed is expanded in these patients and attribute the initial hypotension to this defect. They suggest that copious intravenous fluids can overcome this initial problem. Their data support the hypothesis of an expanded capacitance bed by showing a fall in mean hemoglobin concentration, an increase in plasma volume index but no change in the red cell index with intravenous fluid therapy.[34] If this were the only mechanism in operation, one would expect to see an initial fall in hemoglobin concentration that would remain stable after the vascular space was re-expanded. The continued fall of hemoglobin over one to five days in the absence of blood loss or hemolysis is consistent with further dilutional changes stemming from a progressively expanding vascular bed. This could be a result of over-vigorous intravenous therapy or relate to other continuing neurohumeral mechanisms which cause this vascular bed to continue to expand even as the drug concentration is diminishing. No data exist concerning the renal or endocrine system responses to this clinical situation.

Third, interstitial edema may arise from an increased permeability of the vascular bed induced by a combination of the drug, hypotension, hypothermia, hypoxia and subsequent mechanical

ventilation. If such a defect exists, it would seem likely that copious fluid administration advocated for treatment of hypotension would increase the intravascular hydrostatic pressure and cause an increased leak of fluid.

Without invoking one or more of these hypotheses, it is difficult to understand why in so many presumably healthy young people pulmonary edema develops while fluid loads are being received which would easily be excreted under normal circumstances. This complication of therapy must be seriously considered in the management of these patients until further studies resolve the issue.

• Vigorous attempts have been made to hasten *barbiturate elimination* because it is assumed that the drug is the primary agent which causes the complications we have enumerated. Indications for such measures vary from the total ingested dose to the ingestion of multiple drugs including alcohol (information rarely available to the primary physician) to the serum barbiturate concentration, to the severity of the coma.[15] These data confirm what some authors[2] have previously noted—serum barbiturate concentration is a poor prognostic indicator in these patients. Alcohol and the sedative hypnotic drug should be surveyed in each case. In this series, neither the morbidity nor mortality of any group correlated with drug concentration. Drug withdrawal was not a clinical problem even in those who gave a history of chronic barbiturate abuse. Conversely, half of the patients in Group I were arousable with potentially "lethal concentrations."[14,15] For these reasons we do not feel either the amount of drug ingested or serum drug concentration alone constitutes grounds for aggressive eliminative therapy.

Advocates of vigorous eliminative therapy for severely obtunded patients have yet to present adequately controlled series to show that this technique actually lessens morbidity and mortality.[1] It is doubtful even in those cases where rapid drug removal is possible, that it would have improved the outcome of our deaths due to pneumonia in Group I or II.

Of the effective methods of drug elimination available, dialysis and alkaline diuresis are the most frequently used. Attempting hemodialysis in a hypotensive patient is technically difficult and potentially harmful if blood is shunted from other vital organs. Alkaline forced diuresis over 240 ml per hour invites fluid intolerance as a frequent and potentially lethal complication. Frequent reliable bed scale weights are difficult to obtain in most large clinical facilities, and even 240 ml per hour may prove excessive in some patients. In view of the conflicting data, we have yet to conclude that eliminative measures have a major role in the treatment of these patients.

The basic question which has been neglected in the past is "Why do these patients die?" Our data suggest three major problems in their management: first, pneumonia is the leading cause of morbidity and mortality regardless of the duration or cause of coma; second, over-vigorous hydration in severely obtunded patients is poorly tolerated and may lead to pulmonary edema and death, and, third, additional complications of therapy (pneumothorax, flail chest and so forth) compound an already difficult situation.

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Dealing with Nonspecific Diarrhea

In treating patients with nonbacterial diarrhea, there is no evidence whatsoever that nonabsorbable or absorbable antimicrobial agents produce any sort of beneficial effect. In fact, the reverse is true. Our studies in Central America have again shown that an average patient experiences a prolongation of diarrhea with any type of antimicrobial therapy. And thus, the blind use of diarrhea nostrums containing one or several nonabsorbable antibiotics (which is still widely practiced around the world) is to be condemned. Equally poor practice is the administration of systemic antimicrobial therapy. The situation can really be handled much more effectively by symptomatic treatment.

Most patients with mild to moderate diarrhea probably respond as quickly to rest and to the administration of a bland, clear liquid diet as they do to any type of pharmacologic therapy. Abdominal cramps will often be diminished in frequency or intensity by the local administration of heat—the old hot water bottle is still very useful. Occasionally, anticholinergic agents are beneficial for these complaints. In children, diphenhydramine (Benadryl®)—which combines an antihistaminic action with strong sedative action and an atropine-like effect—is used with reported success by many practitioners in our area for the relief of cramps. It sedates the child, it seems to be quite nontoxic and it has, apparently because of its atropine-like action, an anticramp effect. It, of course, does not affect the diarrhea per se.

I should particularly mention that diphenoxylate, or Lomotil®, should never be employed in small children. I know it is used for this purpose rather widely, but one has to recognize that the range between effective and toxic dosage is too small in young children.

—HEINZ F. EICHENWALD, MD, *Dallas*

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